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Infectious History

Joshua Lederberg

In 1530, to express his ideas on the origin of syphilis, the Italian physician Girolamo Fracastoro penned *Syphilis, sive morbus Gallicus* (Syphilis, or the French disease) in verse. In it he taught that this sexually transmitted disease was spread by "seeds" distributed by intimate contact. In later writings, he expanded this early "contagionist" theory. Besides contagion by personal contact, he described contagion by indirect contact, such as the handling or wearing of clothes, and even contagion at a distance, that is, th spread of disease by something in the air.

Fracastoro was anticipating, by nearly 350 years, one of the most important turning points in biological and medical history—the consolidation of the germ theory of disease by Louis Pasteur and Robert Koch in the late 1870s. As we enter the 21st century, infectious disease is fated to remain a crucial research challenge, one of conceptual intricacy and of global consequence.

The Incubation of a Scientific Discipline

Many people laid the groundwork for the germ theory. Even the terrified masses touched by the Black Death (bubonic plague) in Europe after 1346 had some intimation of a contagion at work. But they lived within a cognitive framework in which scapegoating, say, of witches and Jews, could more "naturally" account for their woes. Breaking that mindset would take many innovations, including microscopy in the hands of Anton van Leeuwenhoek. In 1683, with one of his new microscopes in hand, he visualized bacteria among the animalcules harvested from his own teeth. That opened the way to visualize some of the dreaded microbial agents eliciting contagious diseases.

There were pre–germ-theory advances in therapy, too. Jesuit missionaries in malaria-ridden Peru had noted the native Indians' use of *Cinchona* bark. In 1627, the Jesuits imported the bark (harboring quinine, its anti-infective ingredient) to Europe for treating malaria. Quinine thereby joined the rarified pharmacopoeia—including opium, digitalis, willow (*Salix*) bark with its analgesic salicylates, and little else—that prior to the modern era afforded patients any benefit beyond placebo.

Beginning in 1796, Edward Jenner took another major therapeutic step—the development of vaccination—after observing that milkmaids exposed to cowpox didn't contract smallpox. He had no theoretical insight into the biological mechanism of resistance to the disease, but vaccination became a lasting prophylactic technique on purely empirical grounds. Jenner's discovery had precursors. "Hair of the dog" is an ancient trope for countering injury and may go back to legends of the emperor Mithridates, who habituated himself to lethal doses of poisons by gradually increasing the dose. We now understand more about a host's immunological response to a cross-reacting virus variant.

Sanitary reforms also helped. Arising out of revulsion over the squalor and stink of urban slums in England and the United States, a hygienic movement tried to scrub up

An Infectious Disease Timeline

1346
Black Death begins spreading in Europe.

1492
Christopher Columbus initiates European-American contact, which leads to transmission of European diseases to the Americas and vice versa.

1530
Girolamo Fracastoro puts forward an early version of the germ theory of disease.

1627
Cinchona bark (quinine) is brought to Europe to treat malaria.

1683
Anton van Leeuwenhoek uses his microscopes to observe tiny animalcules (later known as bacteria) in tooth plaque.

1796
Edward Jenner develops technique of vaccination, at first against smallpox.

1848
Ignaz Semmelweis introduces antiseptic methods.

1854
John Snow recognizes link between the spread of cholera and drinking water supplies.

dirt and put an end to sewer stenches. The effort had some health impact in the mid–19th century, but it failed to counter diseases spread by fleas and mosquitoes or by personal contact, and it often even failed to keep sewage and drinking water supplies separated.

It was the germ theory—which is credited to Pasteur (a chemist by training) and Koch (ultimately a German professor of public health)—that set a new course for studying and contending with infectious disease. Over the second half of the 19th century, these scientists independently synthesized historical evidence with their own research into the germ theory of disease.

Pasteur helped reveal the vastness of the microbial world and its many practical applications. He found microbes to be behind the fermentation of sugar into alcohol and the souring of milk. He developed a heat treatment (pasteurization, that is) that killed microorganisms in milk, which then no longer transmitted tuberculosis or typhoid. And he too developed new vaccines. One was a veterinary vaccine against anthrax. Another was against rabies and was first used in humans in 1885 to treat a young boy who had been bitten by a rabid dog.

One of Koch's most important advances was procedural. He articulated a set of logical and experimental criteria, later restated as "Koch's Postulates," as a standard of proof for researchers' assertions that a particular bacterium caused a particular malady. In 1882, he identified the bacterium that causes tuberculosis; a year later he did the same for cholera. Koch also left a legacy of students (and rivals) who began the systematic search for disease-causing microbes: The golden age of microbiology had begun.

> Just as the 19th century was ending, the growing world of microbes mushroomed beyond bacteria. In 1892, the Russian microbiologist Dmitri Ivanowski, and in 1898, the Dutch botanist Martinus Beijerinck, discovered exquisitely tiny infectious agents that could pass through bacteria-stopping filters. Too small to be seen with the conventional microscope, these agents were described as "filtrable [*sic*] viruses."
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> With a foundation of germ theory in place even before the 20th century, the study of infectious disease was ready to enter a new phase. Microbe hunting became institutionalized, and armies of researchers systematically applied scientific analyses to understanding disease processes and developing therapies.

During the early acme of microbe hunting, from about 1880 to 1940, however, microbes were all but ignored by mainstream biologists. Medical microbiology had a life of its own, but it was almost totally divorced from general biological studies. Pasteur and Koch were scarcely mentioned by the founders of cell biology and genetics. Instead, bacteriology was taught as a specialty in medicine, outside the schools of basic zoology and botany. Conversely, bacteriologists scarcely heard of the conceptual revolutions in genetic and evolutionary theory.

Bacteriology's slow acceptance was partly due to the minuscule dimensions of microbes. The microscopes of the 19th and early 20th centuries could not resolve internal microbial anatomy with any detail. Only with the advent of electron microscopy in the 1930s did these structures (nucleoids, ribosomes, cell walls and membranes, flagella) become discernible. Prior to that instrumental breakthrough, most biologists had little, if anything, to do with bacteria and viruses. When they did, they viewed such organisms as mysteriously precellular. It was still an audacious leap for René Dubos to entitle his famous 1945 monograph "The Bacterial Cell."

The early segregation of bacteriology and biology per se hampered the scientific community in recognizing the prospects of conducting genetic investigation with bacteria. So it is ironic that the pivotal discovery of molecular genetics—that genetic information resides in the nucleotide sequence of DNA—arose from studies on serological types of pneumococcus, studies needed to monitor the epidemic spread of pneumonia.

This key discovery was initiated in 1928 by the British physician Frederick Griffith. He found that extracts of a pathogenic strain of pneumococcus could transform a harmless strain into a pathogenic one. The hunt was then on to identify the "transforming factor" in the extracts. In 1944, Oswald Avery, Colin MacLeod, and Maclyn McCarty reported in the *Journal of Experimental Medicine* that DNA was the transforming factor. Within a few years, they and others ruled out skeptics' objections that protein coextracted with the DNA might actually be the transforming factor.

Those findings rekindled interest in what was really going on in the life cycle of bacteria. In particular, they led to my own work in 1946 on sexual conjugation in *Escherichia coli* and to the construction of chromosome maps emulating what had been going on in the study of the genetics of fruit flies, maize, and mice for the prior 45 years. Bacteria and bacterial viruses quickly supplanted fruit flies as the test-bed for many of the subsequent developments of molecular genetics and the biotechnology that followed. Ironically, during this time, we were becoming nonchalant about microbes as etiological agents of disease.

Despite its slow emergence, bacteriology was already having a large impact. Its success is most obviously evidenced by the graying of the population. That public health has been improving—due to many factors, especially our better understanding of infectious agents—is graphically shown by the vital statistics. These began to be diligently recorded in the United States after 1900 in order to guide research and apply it to improving public health. The U.S. experience stands out in charts (see above) depicting life expectancy at birth through the century. The average life-span lengthened dramatically: from 47 years in 1900 to today's expectation of 77 years (74 years for males and 80 for females).* Similar trends are seen

* This sex difference in life expectancy is partly explained by the ability of two X chromosomes to buffer against accumulated recessive mutations and is illustrated by the prevalence in males of color blindness and hemophilia. Another factor is the gender-related difference in self-destructive behaviors.

in most other industrialized countries, but the gains have been smaller in economically and socially depressed countries.

Other statistics reveal that the decline in mortality ascribable to infectious disease accounted for almost all of the improvement in longevity up to 1950, when life expectancy had reached 68. The additional decade of life expectancy for babies born today took the rest of the century to gain. Further improvements now appear to be on an asymptotic trajectory: Each new gain is ever harder to come by, at least pending unpredictable breakthroughs in the biology of aging.

The mortality statistics fluctuated considerably during the first half of the last century. Much of this instability was due to sporadic outbreaks of infections such as typhoid fever, tuberculosis, and scarlet fever, which no longer have much statistical impact. Most outstanding is the spike due to the great influenza pandemic of 1918–19 that killed 25 million people worldwide—comparable to the number of deaths in the Great War. Childhood immunization and other science-based medical interventions have played a significant role in the statistical trends also. So have public health measures, among them protection of food and water supplies, segregation of coughing patients, and personal hygiene. Overall economic growth has also helped by contributing to less crowded housing, improved working conditions (including sick leave), and better nutrition.

As infectious diseases have assumed lower rankings in mortality statistics, other killers—mostly diseases of old age, affluence, and civilization—have moved up the ladder. Heart disease and cancer, for example, have loomed as larger threats over the past few decades. Healthier lifestyles, including less smoking, sparer diets, more exercise, and better hygiene, have been important countermeasures. Prophylactic medications such as aspirin, as well as medical and surgical interventions, have also kept people alive longer.

The 1950s were notable for the "wonder drugs"—the new antibiotics penicillin, streptomycin, chloramphenicol, and a growing list of others that at times promised an end to bacteria-based disease. Viral pathogens have offered fewer routes to remedies, except for vaccines, such as Jonas Salk's and Albert Sabin's polio vaccines. These worked by priming immune systems for later challenges by the infectious agents. Old vaccines, including Jenner's smallpox vaccine, also were mobilized in massive public health campaigns, sometimes with fantastic results. By the end of the 1970s, smallpox became the first disease to be eradicated from the human experience.

Confidence about medicine's ability to fight infectious disease had grown so high by the mid-1960s that some optimists were portraying infectious microbes as largely conquered. They suggested that researchers shift their attention to constitutional scourges of heart disease, cancer, and psychiatric disorders. These views were reflected in the priorities for research funding and pharmaceutical development. President Nixon's 1971 launch of a national crusade against cancer, which tacitly implied that cancer could be conquered by the bicentennial celebrations of 1976, was an example. Few people now sustain the illusion that audacious medical goals like conquering cancer or infectious disease can be achieved by short-term campaigns.

Wake-Up Calls

The overoptimism and complacency of the 1960s and 1970s was shattered in 1981 with the recognition of AIDS. Since then, the spreading pandemic has overtaken one continent after another with terrible costs. Its spread has been coincident with another wake-up call—the looming problem of antibiotic-resistant microbes. This was a predictable consequence of the evolutionary process operating on microbes challenged by the new selection pressure of antibiotics, arising in part from medical prescriptions and in part from unregulated sales and use in feed for crop animals.

AIDS's causative agent, the human immunodeficiency virus (HIV), is a member of the retrovirus family. These viruses had been laboratory curiosities since 1911, when Francis Peyton Rous discovered the Rous sarcoma virus (RSV) in chickens. Early basic research on retroviruses later helped speed advances in HIV research. By the time AIDS began to spread, RSV had been studied for years as a model for cancer biology, because it could serve as a vector for transferring oncogenes into cells. That work accelerated the characterization of HIV as a retrovirus, and it also helped guide our first steps toward medications that slow HIV infection.

AIDS and HIV have spurred the most concentrated program of biomedical research in history, yet they still defy our counterattacks. And our focus on extirpating the virus may have deflected less ambitious, though more pragmatic, aims, including learning to live with the virus by nurturing in equal measure the immune system that HIV erodes. After all, natural history points to analogous infections in simians that have long since achieved a mutually tolerable state of equilibrium.

Costly experiences with AIDS and other infectious agents have led to widespread reexamination of our cohabitation with microbes. Increased monitoring and surveillance by organizations such as the U.S. Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) have revealed a stream of outbreaks of exotic diseases. Some have been due to the new importation of microbes (such as cholera in the Southern Hemisphere); some to older parasites (such as *Legionella*) that have been newly recognized as pathogenic; and some to newly evolved antibiotic-resistant pneumonia strains.

Even maladies that had never before been associated with infectious agents recently have been revealed as having microbial bases. Prominent among these are gastric ulcers,

1860s
Louis Pasteur concludes that infectious diseases are caused by living organisms called "germs." An early practical consequence was Joseph Lister's development of antisepsis by using carbolic acid to disinfect wounds.

1876
Robert Koch validates germ theory of disease and helps initiate the science of bacteriology with a paper pinpointing a bacterium as the cause of anthrax.

1880
Louis Pasteur develops method of attenuating a virulent pathogen (for chicken cholera) so that it immunizes but does not infect; in 1881 he devises an anthrax vaccine and in 1885, a rabies vaccine.

Charles Laveran finds malarial parasites in erythrocytes of infected people and shows that the parasite replicates in the host.

1890
Emil von Behring and Shibasaburo Kitasato discover diphtheria antitoxin serum, the first rational approach to therapy for infectious disease.

1891
Paul Ehrlich proposes that antibodies are responsible for immunity.

1892
The field of virology begins when Dmitri Ivanowski discovers exquisitely small pathogenic agents, later known as viruses, while searching for the cause of tobacco mosaic disease.

1899
Organizing meeting of the Society of American Bacteriologists—later to be known as the American Society for Microbiology—is held at Yale University.

1900
Based on work by Walter Reed, a commission of researchers shows that yellow fever is caused by a virus from mosquitoes; mosquito-eradication programs are begun.

1905
Fritz Schaudinn and Erich Hoffmann discover bacterial cause of syphilis—*Treponema pallidum*.

1911
Francis Rous reports on a viral etiology of a cancer (Rous sarcoma virus).

1918–19
Epidemic of "Spanish" flu causes at least 25 million deaths.

1928
Frederick Griffith discovers genetic transformation phenomenon in pneumococci, thereby establishing a foundation of molecular genetics.

1929
Alexander Fleming reports discovering penicillin in mold.

1935
Gerhard Domagk synthesizes the antimetabolite Prontosil, which kills *Streptococcus* in mice.

which previously had been attributed almost entirely to stress and other psychosomatic causes. Closer study, however, has shown a *Helicobacter* to be the major culprit. Researchers are now directing their speculations away from stress and toward *Chlamydia* infection as a cause of atherosclerosis and coronary disease.

The litany of wake-up calls goes on. Four million Americans are estimated to be infected with hepatitis C, mainly by transfusion of contaminated blood products. This population now is at significant risk for developing liver cancer. Those harboring hepatitis C must be warned to avoid alcohol and other hepatotoxins, and they must not donate blood.

Smaller but lethal outbreaks of dramatic, hypervirulent viruses have been raising public fear. Among these are the Ebola virus outbreak in Africa in 1976 and again in 1995 and the hantavirus outbreak in the U.S. Southwest in 1993. In hindsight, these posed less of a public health risk than the publicity they received might have suggested. Still, studying them and uncovering ecological factors that favor or thwart their proliferation is imperative because of their potential to mutate into more diffusible forms.

Our vigilance is mandated also by the facts of life: The processes of gene reassortment in flu viruses, which are poorly confined to their canonical hosts (birds, swine, and people), goes on relentlessly and is sure to regenerate human-lethal variants. Those thoughts were central in 1997 when the avian flu H5N1 transferred into a score of Hong Kong citizens, a third of whom died. It is likely that the resolute actions of the Hong Kong health authorities, which destroyed 2 million chickens, stemmed that outbreak and averted the possibility of a worldwide spread of H5N1.

Complacency is not an option in these cases, as other vectors, including wildfowl, could become carriers. In Malaysia, a new infectious entity, the Nipah virus, killed up to 100 people last year; authorities there killed a million livestock to help contain the outbreak. New York had a smaller scale scare last summer with the unprecedented appearance of bird- and mosquito-borne West Nile encephalitis, although the mortality rate was only a few percent of those infected. We need not wonder whether we will see outbreaks like these again. The only questions are when and where?

These multiple wake-up calls to the infectious disease problem have left marks in vital statistics. From midcentury to 1982, the U.S. mortality index (annual deaths per 100,000) attributable to infection had been steady at about 30. But from 1982 to 1994, the rate doubled to 60. (Keep in mind that the index was 500 in 1900 and up to 850 in 1918–19 due to the Spanish flu epidemic.) About half of the recent rise in deaths is attributable to AIDS; much of the rest is due to respiratory disease, antibiotic resistance, and hospital-acquired infection.

Our Wits Versus Their Genes

As our awareness of the microbial environment has intensified, important questions have emerged. What puts us at risk? What precautions can and should we be taking? Are we more or less vulnerable to infectious agents today than in the past? What are the origins of pathogenesis? And how can we use deeper knowledge to develop better medical and public health strategies? Conversely, how much more can the natural history of disease teach us about fundamental biological and evolutionary mechanisms?

An axiomatic starting point for further progress is the simple recognition that humans, animals, plants, and microbes are cohabitants of the planet. That leads to refined questions that focus on the origin and dynamics of instabilities within this context of cohabitation. These instabilities arise from two main sources loosely definable as ecological and evolutionary.

Ecological instabilities arise from the ways we alter the physical and biological environment, the microbial and animal tenants (humans included) of these environments, and our interactions (including hygienic and therapeutic interventions) with the parasites. The future of humanity and microbes likely will unfold as episodes of a suspense thriller that could be titled *Our Wits Versus Their Genes*.

We already have used our wits to increase longevity and lessen mortality. That simultaneously has introduced irrevocable changes in our demographics and our own human ecology. Increased longevity, economic productivity, and other factors have abetted a global population explosion from about 1.6 billion in 1900 to its present level above 6 billion. That same population increase has fostered new vulnerabilities: crowding of humans, with slums cheek by jowl with jet setters' villas; the destruction of forests for agriculture and suburbanization, which has led to closer human contact with disease-carrying rodents and ticks; and routine long-distance travel.

Travel around the world can be completed in less than 80 hours (compared to the 80 days of Jules Verne's 19th-century fantasy), constituting a historic new experience. This long-distance travel has become quotidian: Well over a million passengers, each one a potential carrier of pathogens, travel daily by aircraft to international destinations. International commerce, especially in foodstuffs, only adds to the global traffic of potential pathogens and vectors. Because the transit times of people and goods now are so short compared to the incubation times of disease, carriers of disease can arrive at their destination before the danger they harbor is detectable, reducing health quarantine to a near absurdity.

Our systems for monitoring and diagnosing exotic diseases have hardly kept pace with this qualitative transformation of global human and material exchange. This new era of global travel will redistribute and mix people, their cultures, their prior immunities, and their inherited predispositions, along with pathogens that may have been quiescent at other locales for centuries.

This is not completely novel, of course. The most evident precedent unfolded during the European conquest of America, which was tragically abetted by pandemics of smallpox and measles imported into native populations by the invad-

ing armies. In exchange, Europeans picked up syphilis's *Treponema*, in which Fracastoro discerned contagion at work.

Medical defense against the interchange of infectious disease did not exist in the 16th century. In the 21st century, however, new medical technologies will be key parts of an armamentarium that reinforces our own immunological defenses. This dependence on technology is beginning to be recognized at high levels of national and international policy-making. With the portent of nearly instant global transmission of pathogenic agents, it is ever more important to work with international organizations like WHO for global health improvement. After all, the spread of AIDS in America and Europe in the 1980s and 1990s was due, in part, to an earlier phase of near obliviousness to the frightful health conditions in Africa. One harbinger of the kind of high-tech wit we will need for defending against outbreaks of infectious disease is the use of cutting-edge communications technology and the Internet, which already have been harnessed to post prompt global alerts of emerging diseases (see osi.oracle.com:8080/promed/promed.home).

Moving Targets

"Germs" have long been recognized as living entities, but the realization that they must inexorably be evolving and changing has been slow to sink in to the ideology and practice of the public health sector. This lag has early roots. In the 19th century, Koch was convinced that rigorous experiments would support the doctrine of monomorphism: that each disease was caused by a single invariant microbial species rather than by the many that often showed up in culture. He argued that most purported "variants" were probably alien bacteria that had floated into the petri dishes from the atmosphere.

Koch's rigor was an essential riposte to careless claims of interconvertibility—for example, that yeasts could be converted into bacteria. It also helped untangle confusing claims of complex morphogenesis and life cycles among common bacteria. But strict monomorphism was too rigid, and even Koch eventually relented, admitting the possibility of some intrinsic variation rather than contamination. Still, for him and his contemporaries, variation remained a phenomenological and experimental nuisance rather than the essence of microbes' competence as pathogens. The multitude of isolable species was confusing enough to the epidemic tracker; it would have been almost too much to bear to have to cope with constantly emerging variants with altered serological specificity, host affinity, or virulence.

Even today it would be near heresy to balk at the identification of the great plague of the 14th century with today's *Yersinia pestis*; but we cannot readily account for its pneumonic transmission without guessing at some intrinsic adaptation at the time to aerosol conveyance. Exhumations of ancient remains might still furnish DNA evidence to test such ideas.

We now know and accept that evolutionary processes elicit changes in the genotypes of germs and of their hosts. The idea that infection might play an important role in natural selection sank in after 1949 when John B. S. Haldane conjectured that the prevalence of hemoglobin disorders in Mediterranean peoples might be a defense against malaria. That idea developed into the first concrete example of a hereditary adaptation to infectious disease.

Haldane's theory preceded Anthony C. Allison's report of the protective effect of heterozygous hemoglobinopathy against falciparum malaria in Africa. The side effects of this bit of natural genetic engineering are well known: When this beneficial polymorphism is driven to higher gene frequencies, the homozygous variant becomes more prevalent and with it the heavy human and societal burden of sickle cell disease.

We now have a handful of illustrations of the connection between infection and evolution. Most are connected to malaria and tuberculosis, which are so prevalent that genetic adaptations capable of checking them have been strongly selected. The same prevalence also makes their associated adaptations more obvious to researchers. A newly reported link between infection and evolution is the effect of a *ccr5* (chemokine receptor) deletion, a genetic alteration that affords some protection against AIDS. It would be interesting to know what factors—another pathogen perhaps—may

The Microbial World Wide Web

The field of molecular genetics, which began in 1944 when DNA was proven to be the molecule of heredity in bacteria-based experiments, ushered microbes into the center of many biological investigations. Microbial systems now provide our most convenient models for experimental evolution. Diverse mechanisms for genetic variation and recombination uncovered in such systems are spelled out in ponderous monographs. Assays for chemical mutagenesis (e.g., the Ames test using *Salmonella*) are now routinely carried out on bacteria, because microbial DNA is so accessible to environmental insult. Mutators (genes that enhance variability) abound and may be switched on and off by different environmental factors. The germs' ability to transfer their own genetic scripts, via processes such as plasmid transfer, means they can exchange biological innovations including resistance to antibiotics.

Indeed, the microbial biosphere can be thought of as a World Wide Web of informational exchange, with DNA serving as the packets of data going every which way. The analogy isn't entirely superficial. Many viruses can integrate (download) their own DNA into host genomes, which subsequently can be copied and passed on: Hundreds of segments of human DNA originated from historical encounters with retroviruses whose genetic information became integrated into our own genomes.

What makes microbial evolution particularly intriguing, and worrisome, is a combination of vast populations and intense fluctuations in those populations. It's a formula for top-speed evolution. Microbial populations may fluctuate by factors of 10 billion on a daily cycle as they move between hosts, or as they encounter antibiotics, antibodies, or other natural hazards. A simple comparison of the pace of evolution between microbes and their multicellular hosts suggests a millionfold or billionfold advantage to the microbe. A year in the life of bacteria would easily match the span of mammalian evolution!

By that metric, we would seem to be playing out of our evolutionary league. Indeed, there's evidence of sporadic species extinctions in natural history, and our own human history has been punctuated by catastrophic plagues. Yet we are still here! Maintaining that status within new contexts in which germs and hosts interact in new ways almost certainly will require us to bring ever more sophisticated technical wit and social intelligence to the contest. –J.L.

1937
Ernst Ruska uses an electron microscope to obtain first pictures of a virus.

1941
Selman Waksman suggests the word "antibiotic" for compounds and preparations that have antimicrobial properties; 2 years later, he and colleagues discover streptomycin, the first antibiotic effective against tuberculosis, in a soil fungus.

1944
Oswald Avery, Colin MacLeod, and Maclyn McCarty identify DNA as the genetically active material in the pneumococcus transformation.

1946
Edward Tatum and Joshua Lederberg discover "sexual" conjugation in bacteria.

1948

The World Health Organization (WHO) is formed within the U.N.

1952
Renato Dulbecco shows that a single virus particle can produce plaques.

1953
James Watson and Francis Crick reveal the double helical structure of DNA.

Late 1950s
Frank Burnet enunciates clonal selection theory of the immune response.

1960
Arthur Kornberg demonstrates DNA synthesis in cell-free bacterial extract.
François Jacob and Jacques Monod report work on genetic control of enzyme and virus synthesis.

1970
Howard Temin and David Baltimore independently discover that certain RNA viruses use reverse transcription (RNA to reconstitute DNA) as part of their replication cycle.

1975
Asilomar conference sets standards for the containment of possible biohazards from recombinant DNA experiments with microbes.

1979
Smallpox eradication program of WHO is completed; the world is declared free of smallpox.

1981
AIDS first identified as a new infectious disease by U.S. Centers for Disease Control and Prevention.

1982
Stanley Prusiner finds evidence that a class of infectious proteins, which he calls prions, cause scrapie in sheep.

1983
Luc Montagnier and Robert Gallo announce their discovery of the human immunodeficiency virus that is believed to cause AIDS.

1984
Barry Marshall shows that isolates from ulcer patients contain the bacterium later known as *Helicobacter pylori*. The discovery ultimately leads to a new pathogen-based etiology of ulcers.

have driven that polymorphism in earlier human history.

One lesson to be gleaned from this coevolutionary dynamic is how fitful and sporadic human evolution is when our slow and plodding genetic change is pitted against the far more rapidly changing genomes of microbial pathogens.

We have inherited a robust immune system, but little has changed since its early vertebrate origins 200 million years ago. In its inner workings, immunity is a Darwinian struggle: a randomly generated diversification of leukocytes that collectively are prepared to duel with a lifetime of unpredictable invaders. But these duels take place in the host soma; successful immunological encounters do not become genetically inscribed and passed on to future generations of the host. By contrast, the germs that win the battles quickly proliferate their successful genes, and they can use those enhancements to go on to new hosts, at least in the short run.

The human race evidently has withstood the pathogenic challenges encountered so far, albeit with episodes of incalculable tragedy. But the rules of encounter and engagement have been changing; the same record of survival may not necessarily hold for the future. If our collective immune systems fail to keep pace with microbial innovations in the altered contexts we have created, we will have to rely still more on our wits.

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Evolving Metaphors of Infection: Teach War No More

New strategies and tactics for countering pathogens will be uncovered by finding and exploiting innovations that evolved within other species in defense against infection. But our most sophisticated leap would be to drop the manichaean view of microbes—"We good; they evil." Microbes indeed have a knack for making us ill, killing us, and even recycling our remains to the geosphere. But in the long run microbes have a shared interest in their hosts' survival: A dead host is a dead end for most invaders too. Domesticating the host is the better long-term strategy for pathogens.

We should think of each host and its parasites as a superorganism with the respective genomes yoked into a chimera of sorts. The power of this sociological development could not be more persuasively illustrated than by the case of mitochondria, the most successful of all microbes. They reside inside every eukaryote cell (from yeast to protozoa to multicellular organisms), in which they provide the machinery of oxidative metabolism. Other bacteria have taken similar routes into plant cells and evolved there into chloroplasts—the primary harvesters of solar energy, which drive the production of oxygen and the fixed carbon that nourishes the rest of the biosphere.

These cases reveal how far collaboration between hosts and infecting microbes can go. In the short run, however, the infected host is in fact at metastable equilibrium: The balance could tip toward favorable or catastrophic outcomes.

On the bad side, the host's immune response may be excessive, with autoimmune injuries as side effects. Microbial zeal also can be self-defeating. As with rogue cancer cells, deviant microbial cells (such as aggressive variants from a gentler parent population) may overtake and kill the host, thereby fomenting their own demise and that of the parent population.

Most successful parasites travel a middle path. It helps for them to have aggressive means of entering the body surfaces and radiating some local toxicity to counter the hosts' defenses, but once established they also do themselves (and their hosts) well by moderating their virulence.

Better understanding of this balancing act awaits further research. And that may take a shift in priorities. For one, research has focused on hypervirulence. Studies into the physiology of homeostatic balance in the infected host qua superorganism have lagged. Yet the latter studies may be even more revealing, as the burden of mutualistic adaptation falls largely on the shoulders of the parasite, not the host. This lopsided responsibility follows from the vastly different evolutionary paces of the two. But then we have our wits, it is to be hoped, for drafting the last word.

To that end, we also need more sophisticated experimental models of infection, which today are largely based on contrived zoonoses (the migration of a parasite from its traditional host into another species). The test organism is usually a mouse, and the procedure is intended to mimic the human disease process. Instead, it is often a caricature.

Injected with a few bugs, the mouse goes belly up the next day. This is superb for in vivo testing of an antibiotic, but it bears little relation to the dynamics of everyday human disease.

Natural zoonoses also can have many different outcomes. In most cases, there will be no infection at all or only mild ones such as the gut ache caused by many *Salmonella enteritidis* species. Those relatively few infectious agents that cause serious sickness or death are actually maladapted to their hosts, to which they may have only recently gained access through some genetic, environmental, or sociological change. These devastatingly virulent zoonoses include psittacosis, Q fever, rickettsiosis, and hantavirus. Partly through lack of prior coevolutionary development with the new host, normal restraints fail.

I suggest that a successful parasite (one that will be able to remain infectious for a long time) tends to display just those epitopes (antigen fragments that stimulate the immune system) as will provoke host responses that a) moderate but do not extinguish the primary infection, and b) inhibit other infections by competing strains of the same species or of other species. According to this speculative framework, the symptoms of influenza evolved as they have in part to ward off other viral infections.

Research into infectious diseases, including tuberculosis, schistosomiasis, and even AIDS, is providing evidence for this view. So are studies of *Helicobacter*, which has been found to secrete antibacterial peptides that inhibit other enteric infections. We need also to look more closely at earlier stages of chronic infection and search for cross-protective factors by which microbes engage one another. HIV, for one, ultimately fails from the microbial perspective when opportunistic infections supervene to kill its host. That result, which is tragic from the human point of view, is a byproduct of the virus's protracted duel with the host's cellular immune system. The HIV envelope and those of related viruses also produce antimicrobials,

although their significance for the natural history of disease remains unknown.

Now genomics is entering the picture. Within the past decade, the genomes of many microbes have been completely sequenced. New evidence for the web of genetic interchange is permeating the evolutionary charts. The functional analyses of innumerable genes now emerging are an unexplored mine of new therapeutic targets. It has already shown many intricate intertwinings of hosts' and parasites' physiological pathways. Together with wiser insight into the ground rules of pathogenic evolution, we are developing a versatile platform for developing new responses to infectious disease. Many new vaccines, antibiotics, and immune modulators will emerge from the growing wealth of genomic data.

The lessons of HIV and other emerging infections also have begun taking hold in government and in commercial circles, where the market opportunities these threats offer have invigorated the biotechnology industry. If we do the hard work and never take success for granted (as we did for a while during the last century), we may be able to preempt infectious disasters such as the influenza outbreak of 1918–19 and the more recent and ongoing HIV pandemic.

Perhaps one of the most important changes we can make is to supercede the 20th-century metaphor of war for describing the relationship between people and infectious agents. A more ecologically informed metaphor, which includes the germs'-eye view of infection, might be more fruitful. Consider that microbes occupy all of our body surfaces. Besides the disease-engendering colonizers of our skin, gut, and mucous membranes, we are host to a poorly cataloged ensemble of symbionts to which we pay scant attention. Yet they are equally part of the superorganism genome with which we engage the rest of the biosphere.

The protective role of our own microbial flora is attested to by the superinfections that often attend specific antibiotic therapy: The temporary decimation of our home-team microbes provides entrée for competitors. Understanding these phenomena affords openings for our advantage, akin to the ultimate exploitation by Dubos and Selman Waksman of intermicrobial competition in the soil for seeking early antibiotics. Research into the microbial ecology of our own bodies will undoubtedly yield similar fruit.

Replacing the war metaphor with an ecological one may bear on other important issues, including debates about eradicating pathogens such as smallpox and polio. Without a clear strategy for sustaining some level of immunity, it makes sense to maintain lab stocks of these and related agents to guard against possible recrudescence. An ecological perspective also suggests other ways of achieving lasting security. For example, domestication of commensal microbes that bear relevant cross-reacting epitopes could afford the same protection as vaccines based on the virulent forms. There might even be a nutraceutical angle: These commensal epitopes could be offered as optional genetically engineered food additives, clearly labeled and meticulously studied.

Another relevant issue that can be recast in an ecological model is the rise in popularity of antibacterial products. This is driven by the popular idea that a superhygienic environment is better than one with germs—the "enemy" in the war metaphor. But too much antibacterial zeal could wipe out the very immunogenic stimulation that has enabled us to cohabit with microbes in the first place.

Ironically, even as I advocate this shift from a war metaphor to an ecology metaphor, war in its historic sense is making that more difficult. The darker corner of microbiological research is the abyss of maliciously designed biological warfare (BW) agents and systems to deliver them. What a nightmare for the next millennium! What's worse, for the near future, technology is likely to favor offensive BW weaponry, because defenses will have to cope with a broad range of microbial threats that can be collected today or designed tomorrow.

As a measure of social intelligence and policy, we should push for enforcement of the 1975 BW disarmament convention. The treaty forbids the development, production, stockpiling, and use of biological weapons under any circumstances. One of its articles also provides for the international sharing of biotechnology for peaceful purposes. The scientific and humanistic rationale is self-evident: to enhance and apply scientific knowledge to manage infectious disease, naturally occurring or otherwise.

Further Readings

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Notable Web Sites

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www.idsociety.org
www.asmusa.org
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www.cdc.gov/ncidod/EID

Joshua Lederberg is a Sackler Foundation Scholar heading the Laboratory of Molecular Genetics and Informatics at The Rockefeller University in New York City, and a Nobel laureate (1958) for his research on genetic mechanisms in bacteria. He has worked closely with the Institute of Medicine and the Centers for Disease Control and Prevention on analytical and policy studies on emerging infections.

1985
Robert Gallo, Dani Bolognesi, Sam Broder, and others show that AZT inhibits HIV action in vitro.

1988
Kary Mullis reports basis of polymerase chain reaction (PCR) for detection of even single DNA molecules.

1995
J. Craig Venter, Hamilton Smith, Claire Fraser, and colleagues at The Institute for Genomic Research elucidate the first complete genome sequence of a microorganism: *Haemophilus influenzae*.

1996
Implied link between bovine spongiform encephalopathy ("mad cow disease") and human disease syndrome leads to large-scale controls on British cattle.

1999
New York City experiences outbreak of West Nile encephalopathy transmitted by birds and mosquitoes.

c 2000
Antibiotic-resistant pathogens are spreading in many environments.

For more extensive chronological listings, see "Microbiology's fifty most significant events during the past 125 years," poster supplement to *ASM News* 65(5), 1999.